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Modern Perspectives on Adiponectin: Targeting Obesity, Diabetes, and Cancer Together Using Herbal Products

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Abstract: Obesity, Diabetes, and Cancer are major health concerns worldwide. Studies are ongoing to find a molecular drug target that simultaneously regulates these diseases. One such protein is adiponectin which modulates numerous physiological processes and regulates pathways associated with these diseases. Here we have reviewed the potential of adiponectin as a drug target and discussed possible mechanisms by which herbal compounds can modulate its function. Adiponectin exerts its function by binding to its transmembrane receptors (adipoR1 and adipoR2), which stimulate signaling cascades involved in regulating these diseases. Adiponectin activity can be enhanced by the transcription factor, peroxisome proliferator-activated receptor gamma (PPARγ), or several natural compounds(like curcumin). The mechanism by which these phytocompounds influence adiponectin activity at the molecular level is unclear. Here we have summarized various natural compounds that can modulate adiponectin activity and *in silico*, examined the mechanism by which curcumin regulates adiponectin activity. Our molecular docking studies results indicate that curcumin can act as a ligand for PPARγ and activate adiponectin. Understanding the adiponectin activation mechanism will help develop new herbal drugs to cure obesity, diabetes, and cancer.

Keywords: adiponectin; curcumin; PPARγ; molecular docking; natural compounds; obesity; diabetes; cancer.

1. Introduction

Adiponectin is the most abundant adipokine secreted by the white adipose tissues through adipocytes into the bloodstream in the form of oligomeric derivatives such as trimeric:67 kDa, hexameric:140 kDa, and high molecular weight polymeric:300 kDa with distinct features of these oligomeric form[1]. It ameliorates insulin sensitivity, reduces inflammation oxidative stress, and regulates metabolic diseases [2-4]. The protein is a biomarker for several conditions like obesity, diabetes, aging, and cardiovascular diseases [5].

It plays a key role in maintaining the male and female reproductive system [6] and regulating the pathophysiology of several diseases in the liver and skeletal muscle.

The protein acts on adipoR1 and adipoR2 receptors, which exist as isoforms, initiating the downstream signaling mechanism. Many adiponectin mimics [7] can also bind to these receptors and lead to signaling, as in the case of adiponectin. Prominent one of these receptor agonists is AdipoRon [8] which can be used to treat various physiological diseases. It needs to be extensively studied how these natural compounds modulate the adiponectin signaling pathway [9,10]. Several dietary compounds can also activate adiponectin like curcumin. A schematic representation of the adiponectin signaling pathway is shown in Fig. 1. The amount of circulating adiponectin is observed to be increased drastically in patients with a curcumin diet [11]. Here we have reviewed various natural compounds that can enhance adiponectin activity. Further, using curcumin as an example and molecular docking technique, we have explored the possible mechanisms by which it can modulate adiponectin activity.

The adipoR1 and adipoR2 are seven-transmembrane helical proteins similar to G-protein─coupled receptors (GPCRs) [12] with reversed polarity for C-and N-terminals. As biological membranes play a key role in a number of these cases [13,14], like curvature changes or hydrophobic mismatching [15], the role of biological membranes in adiponectin signaling needs to be considered to be explored. Here we have discussed possible mechanisms by which membranes may modulate this signaling pathway. A good understanding of this pathway will open avenues in pharmacy to develop new therapeutic drugs that can treat multiple diseases like cancer, cardiovascular disorders, obesity, and diabetes all at once.

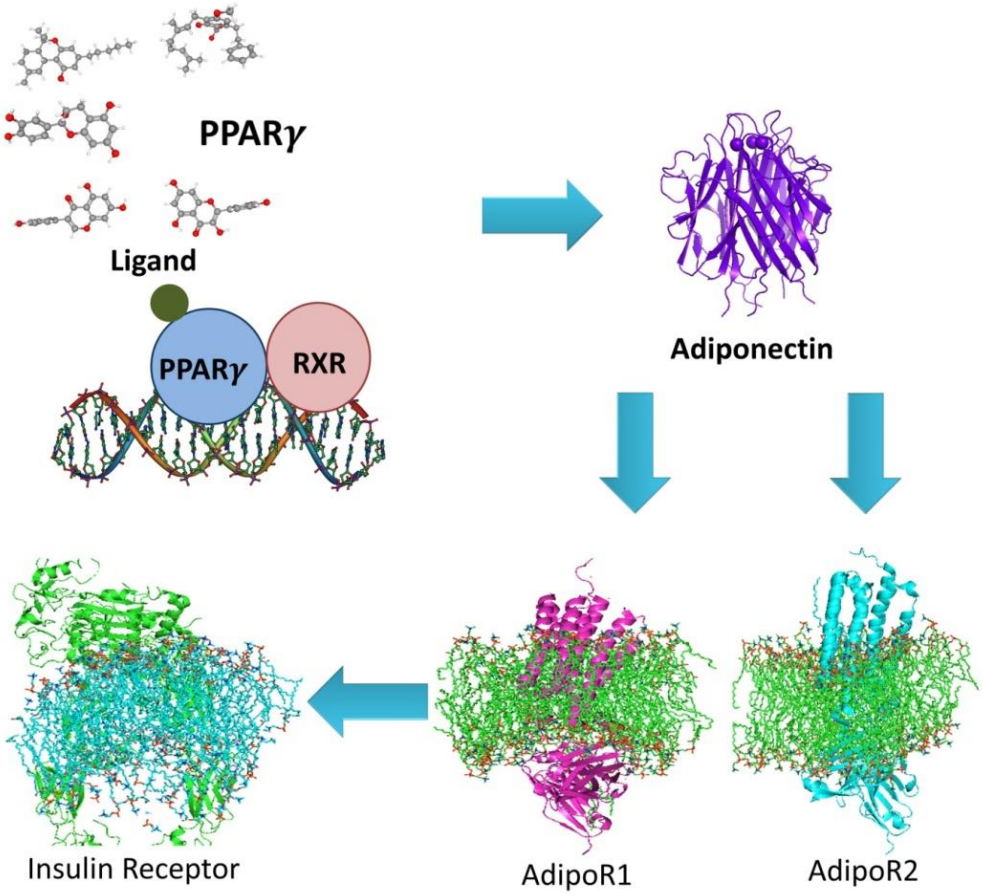

Figure 1. Schematic representation: The adiponectin signaling cascade initiates when the protein acts on its receptor AdipoR1 and AdipoR2, which further activates downstream signaling and pathways involved in obesity, diabetes, and cancer regulation. The transcription factor (PPARγ) and natural compounds can modulate adiponectin activity.

1.1. Adiponectin structure.

The full-length protein consists of 244 amino acids and is made up of four domains: a signal peptide domain ranging from amino acid 1 to 18, a hypervariable domain from 19 to 41 amino acids, a collagen-like fibrous domain constituting of 66 amino acids, and a C-terminal globular domain from 108-244 amino acids [1,16]. The function of the signal peptide domain is to secrete the hormone outside of the cell. The succination (non-enzymatic post-translational modification of cysteine (Cys36 in this case) residue) in the hypervariable region of the protein prevents the oligomerization state. Hence, this region is most active in the case of diabetic patients [1]. The highly ordered oligomers formation occurs in the collagenous domain. The formation of globular adiponectin (produced from the proteolysis of full-length protein) occurs in the C1q (C-terminal globular) domain. This proteolytically cleaved product is also active. The X-ray crystallography, cryo-EM studies, and other structural studies have greatly helped understand the adiponectin signaling pathway. The examples of the PDB (Protein Data Bank) structures available for adiponectin and different partners involved in its signaling pathway are depicted in Fig. 2.

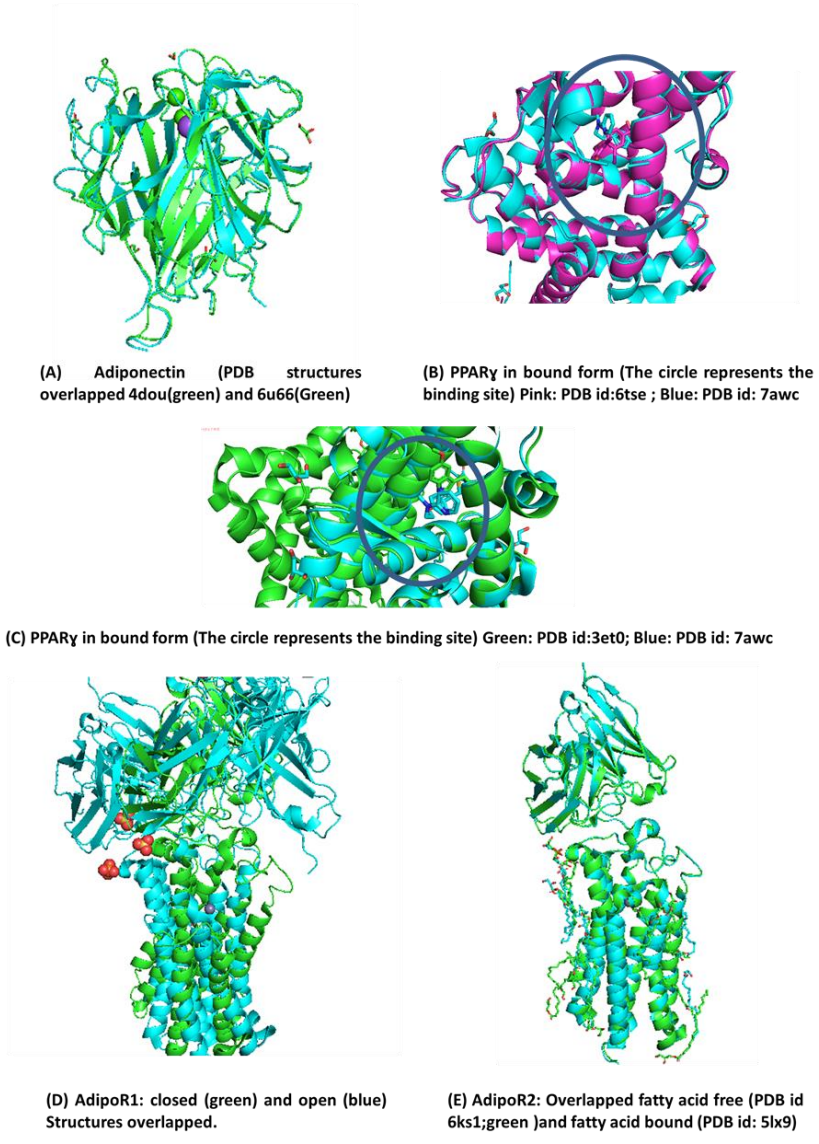

Figure 2. Comparison of different structures available in protein data bank.

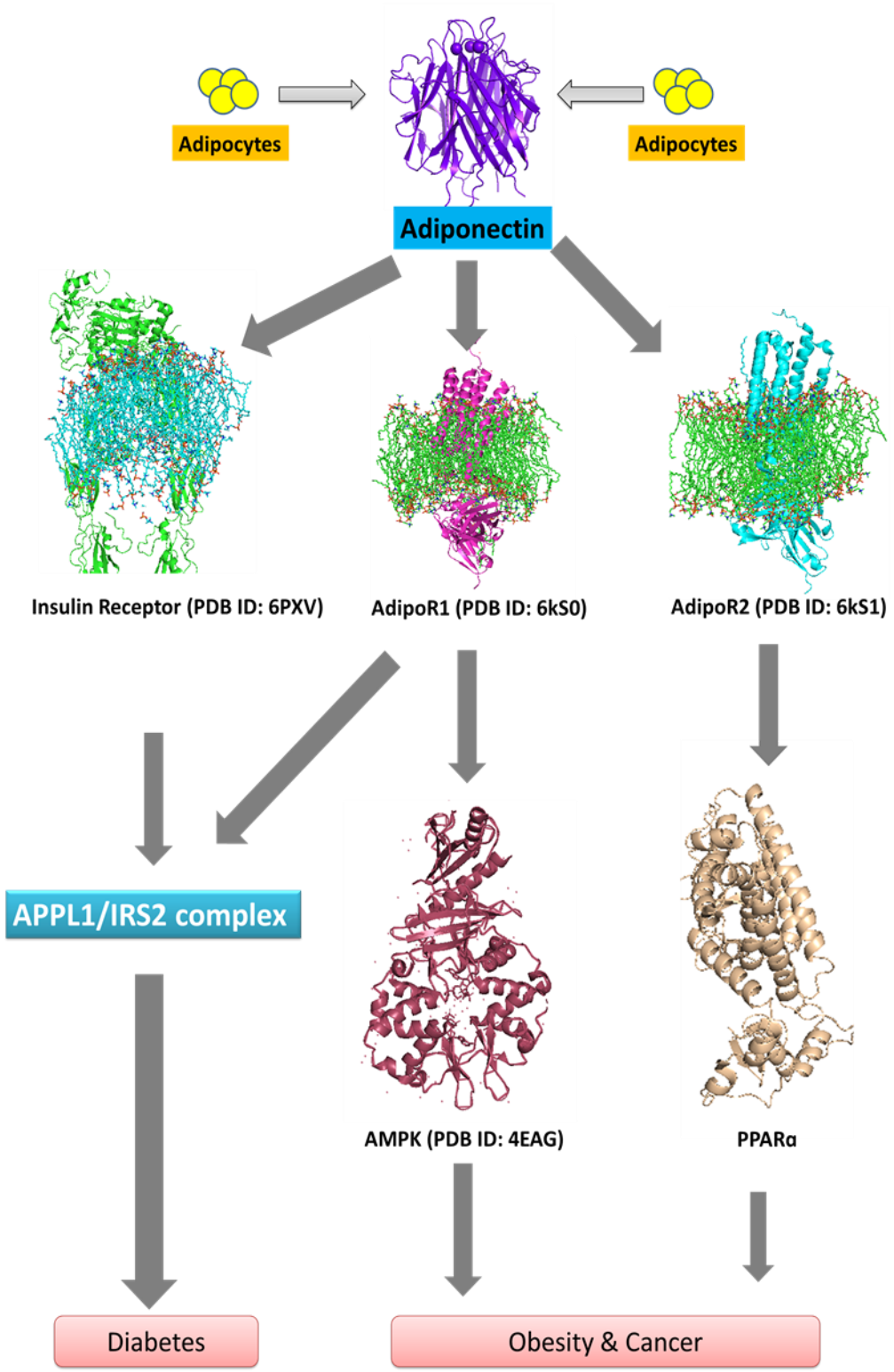

Figure 3. Representation of adiponectin signaling pathway and key players involved in achieving the biological response.

1.2. Role of oligomerization in adiponectin functioning.

Adiponectin exists in different forms viz higher molecular weight (HMW) (12─36 units), hexameric low-molecular-weight, and the trimeric form [6]. These different forms are related to various biological activities. The HMW form is related to lower adiposity and lower chances of the prevalence of type-2 diabetes [8,9]. The possibility of the HMW form being

active while the hexameric and trimeric forms their proteolytic products still need to be investigated. The HMW form is more prominent in women than men [7].

The structural organization of adiponectin is important in modulating its function. As mentioned above, adiponectin exhibits different oligomeric states with different functions. For example,adiponectin enhances nuclear factor-κB (NFκB) activation through high molecular weight forms [11,16]. Adiponectin also exhibits anti-inflammatory activity by improving nuclear factor-κB (NFκB) activation [17-19]. Similarly, The T-cadherin (an additional receptor for adiponectin) can function exclusively with hexameric and HMW forms of adiponectin [20]. T-cadherins were observed for their function chiefly in cell growth, survival, and proliferation phenomenons. *In-vitro* studies have shown that the dysregulation of the molecule can lead to several cancers. Interestingly, the oligomerization of this protein is not attributed to its hydrophobicity since the GRAVY (Grand average of hydropathicity) index of the protein is -0.41, which is an indicator of its hydrophilic nature. The pair of chaperons present in the endoplasmic reticulum (ER), namely ERp44 (ER protein with MW44 kDa) and Ero1-Lalpha (ER oxidoreductase 1-Lα), regulates the oligomerization state of adiponectin. Hydroxylation and glycosylation are some of the post-translational modifications required to stabilize a higher-order oligomeric state [13]. How the metal ions [14] and disulfide bonds [15] result in the formation of an oligomeric state still need to be studied further.

1.3. Adiponectin signaling mechanism and connection to diabetes, obesity, and cancer.

There are three different major pathways by which adiponectin stimulates a biological response. The Adaptor Protein, Phosphotyrosine Interacting with pH Domain and Leucine Zipper 1 (APPL1) protein acts as an adaptor molecule in the pathways involved in the regulation of insulin and lipid metabolism. There is a crosstalk between APPL1, adiponectin signaling product, and insulin receptor substrate in the first binding mode. This mediator molecule directly binds to insulin receptor substrate 1 and 2 (IRS1/2), which in turn subsequently activates phosphatidylinositol 3-kinase (PI3K), PDK1(3-Phosphoinositide-dependent kinase 1), AKT or Protein Kinase B (PKB), FOXO1 (Forkhead box protein O1), and biological response (increase in glycolysis and decrease in gluconeogenesis) [21]. In this way, adiponectin is involved in the regulation of diabetes (Fig. 3). Further, the adiponectin acts as a ligand for the adipoR1 receptor (Fig. 3). This adiponectin receptor predominantly found in skeletal muscles has a high affinity for globular protein.

The over-expression of the adipoR1/R2 receptor in the liver is associated with exacerbating liver ceramide level and ameliorating insulin sensitivity levels. The adiponectin binds to the adipoR1 receptor and leads to conformational changes. There is a movement of helices IV and V of 3.6 Å and 11 Å, respectively, upon ligand binding [22]. This conformation is known as the open conformation—the adaptor protein APPL1 associates with the adipoR1 receptor via the COOH-terminal PTB domain [23]. The binding of this molecule is followed by activation of protein phosphatase 2A and subsequently dephosphorylation of the LKB1 (liver kinase B1) enzyme. This enzyme moves from the nucleus to the cytoplasm and activates the AMPK (AMP-activated protein kinase) enzyme by phosphorylation. This is a very important step in the adiponectin signaling pathway. This enzyme is involved in several pathways important in physiological processes. The association of this enzyme with adiponectin and how it links to GPCRs has been discussed later in this review.

The activated AMPK stimulates numerous pathways like ACC (acetyl-CoA carboxylase), eNOS (Endothelial nitric oxide synthase), IKK/NFκB/PTEN, mTOR, PGC1α,

and FOXO3 signaling pathways. The ACC pathway is involved in an increase in fatty acid oxidation (decrease in fatty acid synthesis) and energy expenditure. Thus the, adiponectin plays a key role in controlling obesity. The AMP phosphorylation is followed by activation of the eNOS pathway, leading to vasodilation and further blood flow in the section lacking oxygen. The halting of the IKK/NFκB pathway is one of the newest approaches currently used in cancer therapy [24]. The activated AMPK leads to inhibition of this pathway that prevents IKK/NFκB/PTEN stimulated apoptosis and causes cytoprotection. The mTOR (mammalian target of rapamycin) pathway is another target for activated AMPK enzymes. This pathway plays a key role in cell metabolism, growth, and survival. This pathway is also one of the therapeutic targets for colorectal cancer [25]. Therefore the role of adiponectin can be very important in curing cancer. The other pathways switched on after AMPK phosphorylation are PGC1α [26,27] and FOXO3 [28] signaling pathways. They are involved in increasing mitochondrial biogenesis. The Rab5 is a small GTPase that is crucial in carrying substances from the plasma membrane to early endosomes [29]. The activation of Rab5 is associated with the internalization of GLUT4 (a glucose transporter) and glucose uptake. The reduced GLUT4 transport is related to insulin resistance [29,30] and thus type II diabetes. This is another mode of action through which adiponectin signaling controls diabetes.

In another pathway by which adiponectin regulates fatty acid oxidation, just as in the case of adipoR1 here, also APPL1 acts as an adaptor molecule [21-24]. The APPL1 drastically improves PPARα expression, an important transcription factor regulating metabolism. This, in turn, escalates acetyl coenzyme A oxidase (ACO) and uncoupling proteins, resulting in fatty acid oxidation. Another mechanism where adiponectin acts as a ligand includes T-cadherin receptor correlated signaling. It was observed that only high molecular weight (HMW) and hexameric forms of adiponectin interact with T-cadherin, which implies this pathway operated in the eukaryotic system. This molecule regulates smooth muscle cell vasculature [31] and prevents neointima proliferation and atherosclerosis [29]. It is also found that adiponectin exerts its effects to prevent cardiovascular diseases [32] and may play an important role in modulating cytokine storm in COVID-19 disease [33]. To summarize, adiponectin is a very important protein that plays a key role in several diseases, and understanding the system will help in drug development.

1.4. Adiponectin crosstalk with peroxisome proliferator-activated receptor.

An inflow of glucose in the adipose cells activates adiponectin [28]. The activation of transcription factors peroxisome proliferator-activated receptor alpha (PPARα) [34] and peroxisome proliferator-activated receptor-gamma (PPARγ) has been found to stimulate this adipokine [35]. There has been a direct correlation between PPARγ and adiponectin hormone levels. This transcription factor typically gets stimulated by the binding of ligands [36]. Several PPARγ agonists like thiazolidinedione (TZD) have increased circulating adiponectin activity by 5 to 10 times [37]. The mechanism by which PPARγ activates adiponectin is that it attaches to PPAR response elements (or PPREs), a particular DNA sequence found in the vicinity of the transcriptional start site of genes. This is followed by the recruitment of transcriptional coregulators that change local chromatin structure, stimulate the competent RNA polymerase complex congregation, and initiate transcription of the genes.

In the case of the binding of PPARγ agonist, the binding of the ligand to the ligand-binding domain (LBD) of the protein leads to its conformational change, which dissociates it from the co-repressors (NCoR and SMRT). The function of these receptors is to halt the gene

transcription activity, and once it gets dissembled, the transcriptional activity continues [38]. Another transcription factor (PPARα) is also associated with enhancing adiponectin action. The activation pathway for PPARα agonist is independent of that of PPARγ [39]. The PPARα agonist, Wy-14,643, has been shown to increase the activity of adipoR receptors and thus increase adiponectin action.

1.5. Adiponectin as a drug target and its distinct relation to G-Protein-Coupled Receptors (GPCRs).

Adiponectin is one of the potential drug targets against obesity, diabetes, and cancer. The protein exerts its activity specifically in the liver, skeletal muscles, and vasculature. Several studies suggest that adiponectin replacement therapy might be useful in treating multiple diseases, as mentioned above [1]. Adiponectin is also distinctly related to G-Protein-Coupled Receptors (GPCRs), which are one of the major thrust areas in the field of biochemistry. These GPCRs are involved in major cellular functions like heartbeat regulation and vision—about 40 % of the drugs target GPCRs to treat diseases. The GPCRs are related to adiponectin *via* a sensor of a common energy regulatory AMP-activated protein kinase (AMPK). It is an important metabolic enzyme activated by some GPCRs like adrenoreceptors and cannabinoid receptors [40]. The AMPK maintains cellular homeostasis, and its activators can be used as therapeutic agents in many diseases [41]. Although AMPK is related to many physiological processes, it is not the best drug target since it lacks a tissue-specific effect.

2. *In silico* Studies with Adiponectin and Subsequent Molecules in Adiponectin Signaling

Adiponectin is a small molecular weight protein hormone involved in regulating multiple diseases, so it might seem a good candidate for computational docking studies. However, it exhibits multiple forms, including very high molecular weight forms, and it is challenging to work on in silico studies with adiponectin HMW species. Therefore, only a limited number of computational studies are performed with this system. The amino acid mutational studies can be performed using computational tools to identify the critical amino acids involved in adiponectin function related to HMW species. The crucial role of Arg131 residue in protein oligomerization has been demonstrated using computational studies [42].

There have been molecular docking [43] and Molecular Dynamics (MD) simulations [44] studies conducted to screen for adiponectin mimic or AdipoRs agonist. A few compounds identified can act like adiponectin, which binds to AdipoRs and activates downstream adiponectin signaling. The exact molecular mechanism by which these compounds can activate downstream signaling is not very well understood. However, possibly these AdipoRs agonists viz. AdipoRon [45] and ADP355 [46] bind to these membrane receptors. Upon binding, they lead to a conformational change in AdipoR1/R2 as in the case of adiponectin and stimulate the downstream signaling *via* PPARα and AMPK phosphorylation. AdipoRon has a low binding affinity to its receptors, having a dissociation constant in the μM range. Thus extensive computational and in vitro studies can be performed to screen for the AdipoRon derivatives, which can bind with higher affinity to AdipoR1/R2 receptors. A good quality crystal structure of adiponectin receptors (2.9 Å and 2.4 Å for Adipo R1 and adipoR2, respectively) is available, which can immensely help perform these computational studies [47-50].

PPARs (Peroxisome proliferator-activated receptors)are a group of transcription factors stimulated by its agonist. The PPARα and PPARγ are two of its members involved in adiponectin signaling. The PPARγ is present upstream of adiponectin signaling, whereas

PPARα is present downstream of the signaling. Thiazolidinediones (TZDs) are known agonist of PPARγ, but it has side effects [51]. Furthermore, to overcome these side effects, natural bioactive/ayurvedic/herbal extracts and derived compounds need to be screened that can act as an agonist to PPARγ protein. Several polyphenols [52] and compounds from *Rhizophora apiculata* [53] have been found to possess a binding affinity for PPARγ receptors. Many other secondary metabolites/compounds like curcumin have increased serum adiponectin levels [54]. One possible pathway that can be tested in silico is that these compounds can bind to PPARγ and stimulate its activity, increasing adiponectin activity. We have discussed this possibility in the section below. The second member of this transcription factor family PPARα acts downstream of the pathway and regulates fatty acid oxidation and energy homeostasis. Phenoxazinones [55] and Kojyl cinnamate esters [56] are some PPARα agonists enhancing adiponectin signaling. The in silico and in vitro analysis can reveal the exact molecular mechanism these agonists work. Another important protein kinase that plays a key role in adiponectin signaling is the AMPK enzyme. The phosphorylation of this is required for its activation. This energy biosensor also regulates many processes downstream of adiponectin signaling. Computational studies are being done to screen for the compounds that can activate this enzyme [57,58]. Catechin and licochalcone-A are a couple of compounds that have been shown to exhibit AMPK activation activity (Fig. 4) [59].

3. Natural Bioactive Compounds that Can Regulate Adiponectin Signaling

Several dietary and herbal compounds have been discovered to regulate the adiponectin pathway [60]. These compounds can act via different pathways and target different adiponectin signaling pathway components. Several natural compounds can enhance the downstream adiponectin pathway by activating adiponectin receptors just like adiponectin. These compounds fall into the category called adiponectin mimics [61]. The lifestyle modifications are also associated with increased adiponectin levels [62-64]. The molecular mechanism by which these herbal compounds stimulate adiponectin signaling has been studied for some of these compounds. In contrast, for some natural compounds, it is still a matter of research.

3.1. Natural compounds acting on PPARγ.

A considerable number of dietary products reported can activate PPARγ and increase circulating adiponectin secretion. Amorfrutin is one of these natural products derived from Amorphafruticosa, a flowering plant belonging to Fabaceae legume plants, which has been shown to increase the adiponectin expression in vitro [65]. They act upon PPARγ and stimulate the transcription genes involved in the adiponectin signaling pathway. Astragaloside II and Isoastragaloside I are compounds extracted from the herbal plant Radix Astragali and have been shown to selectively elevate adiponectin production in 3T3-L1 and primary mouse adipocytes [64]. Some of these astragalosides are known to be PPARγ agonists [65-67], and it is possible that they also target PPARγ for its activity [68,69]. Catechin is observed as another PPARγ activator [70,71] can also increase circulating HMW adiponectin concentration [72]. Catechin and relevant phytochemicals have been found to be effective for promoting transcription factors that they activate or inhibit (e.g., NF-κB, PPARγ) [73-75]. Tetrahydrocannabinol, kaempferol, quercetin, genistein, and amorfrutins are other herbal compounds that stimulate the adiponectin pathway [76-78]. Goto et al. performed a deep study

of phytochemicals, bixin, to evaluate its applicability to activate PPARα and found improved obesity-induced abnormalities of metabolism for carbohydrates and lipids in mice [79].

3.2. Natural compounds acting on PPARα.

Rigano et al. described that PPARα agonists could also escalate adiponectin signaling by a mechanism independent of PPARγ [80]. Bixin is one of the naturally occurring PPARα activators which can help in ameliorating obesity [79]. The extract of *Ephedra species* acts as herbal medicine against obesity by increasing PPARα concentration [81-84]. Carotenoids are also phytoproducts and another PPARα agonist that has been associated in direct relation with HMW adiponectin concentration [1,19]. Some naturally occurring flavonoids like hesperetin and naringenin act upon PPARα and improve adipocyte activity [85-87]. A depiction of different herbal compounds targeting PPARα and PPARγ is shown in Fig.4. In this study, PPARα activators were found significantly effective for obesity control through carbohydrate metabolism by the oxidation of fatty acids in the liver. In addition, it was noticed that the dietary cis derivatives of carotenoids had been wide applicabilities as coloring agents in food and textile industries [88-90], mainly bixin and norbixin, have been reported to the activation of PPARα by luciferase assays using GAL4/PPARα chimeric and full-length PPARα. The molecular mechanism by which these agonists act is not clearly understood. In addition, the structural changes associated with PPARα binding to its agonists can be studied extensively shortly. The information will be useful in generating effective drugs from natural products to boost adiponectin signaling.

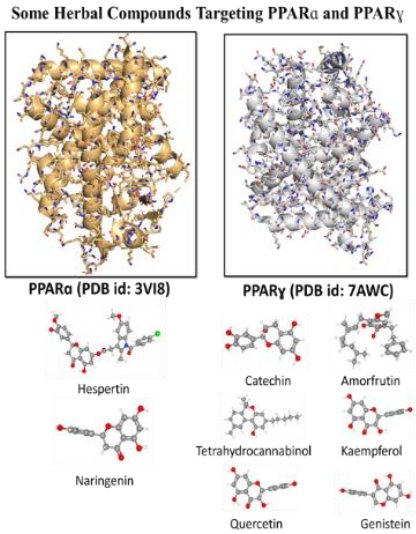

Figure 4. Depiction of compounds extracted from natural bioactive sources targets either PPARα or PPARϒ for stimulating adiponectin signaling.

4. *In silico* Analysis of the Possible Mode of Action of Natural Compounds on how it Increases Circulating Adiponectin Concentrations

Several dietary compounds have been shown to increase circulating adiponectin levels, but their mechanism of action is not well known. The compounds, including curcumin derived from turmeric [91,92], ingredients of ginger and red pepper, gingerol, and capsaicin [93], are found ethnomedicinal important to cure cancer, obesity, diseases [94-98]. There are several different mechanisms by which these compounds can exert their effects. They can act upon PPARγ and activate the transcription factor. Secondly, they can associate with adiponectin and

enhance its production. To intensify the adiponectin signaling pathway, they can also act on adipoR1 and adipoR2 receptors [98,99]. It may also have a multimode action mechanism where the dietary compound can interact with different receptors and increase adiponectin activation. In this mode of action, a synergetic effect (because of the combination of two different effects) will be seen. The net outcome will be achieved by combining the effects from individual interactions.

Here we have conducted an *in silico* analysis to examine the possible mode of action of these natural compounds using curcumin as an example. We investigated the binding affinity of curcumin with PPARγ, adiponectin, adipoR1, and adipoR2 receptors, respectively, using the swiss dock online server. The PPARγ is a known agonist of adiponectin. We also wanted to check if curcumin can bind and activate adiponectin, so we also examined the binding affinity of curcumin to adiponectin. Lastly, to study if curcumin can act as an adiponectin mimic, we investigated the binding affinity of curcumin with adipoR1 and adipoR2. We generated a 3D computational model of adiponectin (QMEAN -1.34) and PPARγ (QMEAN -2.52) using the Swissdock model. The primary sequence was extracted from UniProt. The molecular docking studies were conducted using an online swiss dock online server. We compared the ΔG values of these interactions to check the binding affinity of curcumin with them. The binding site was predicted using a .pdb structure already known. We found the curcumin has the highest binding affinity with PPARγ which is about -9.03 KJ/mol (Fig. 5) compared to adiponectin (ΔG =-7.47 KJ/mol), adipoR1 = 7.62 KJ/mol, adipoR2 = -7.37 KJ/mol). There is an insignificant difference between the binding affinity of curcumin with the other three potential candidates. Our results found that curcumin acts as a PPARγ agonist and stimulates circulating adiponectin serum levels. It is also possible that curcumin might be functioning by a multimode mechanism[100]. In addition to acting as an agonist, it is also binding to the adipoR1, adipoR2 receptors, or adiponectin to activate it. An extensive study needs to be conducted to examine its mechanism further.

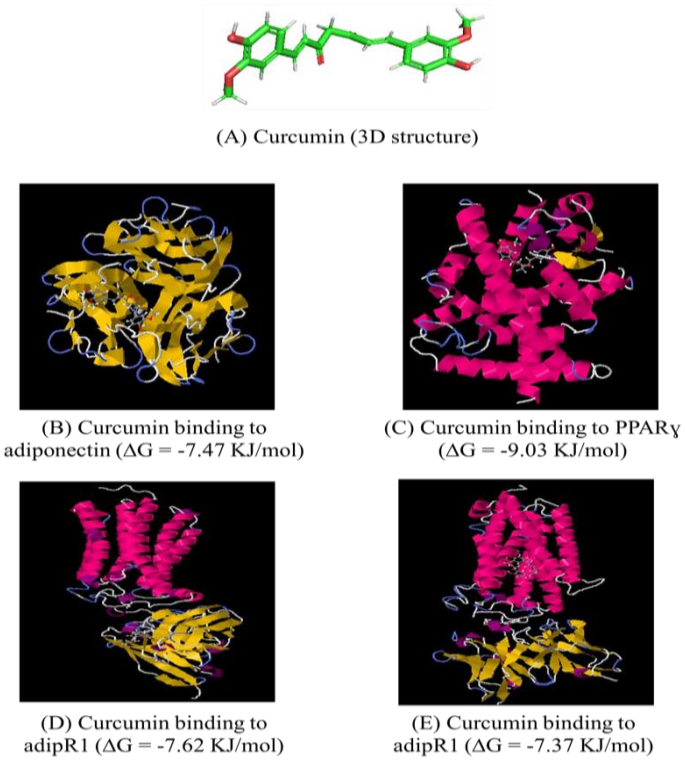

Figure 5. The binding affinity of curcumin with different potential candidates.

5. Conclusion and Future Direction

Adiponectin is a protein hormone involved in regulating multiple diseases like obesity, diabetes, and cancer and can act as a potential drug target against these diseases simultaneously. The protein exhibits different oligomeric forms, which are associated with different functions. Various synthetic drugs (line TZD) have been discovered to stimulate the adiponectin signaling pathway, but they have side effects, which is a concern. Studies are being shifted to examine natural bioactive compounds that ameliorate adiponectin signaling. These herbal compounds can act upstream of the pathway, like in the case of PPARγ agonist, or downstream of the pathway like the PPARα activator. They may also act like adiponectin mimics. Various natural compounds have been shown to have a positive regulatory effect on adiponectin with the increase in circulating adiponectin levels.

However, the molecular mechanism by which these compounds act is not clearly understood. Here we have conducted *in silico* studies and performed molecular docking using curcumin as a prototype to unveil the possible mechanism by which these natural compounds may enhance adiponectin signaling. We studied the binding of curcumin with different receptors and examined the binding energy of the interaction. Based on the binding affinity results, we believe these compounds can bind to PPARγ and activate it to stimulate adiponectin signaling. It is also possible that curcumin might also be interacting with other receptors in a multimode action to stimulate adiponectin signaling. In the future, *in-vitro* and in vivo studies can be conducted extensively to explore the effect of these herbal products on the adiponectin pathway. Understanding this system will help develop new drugs using natural compounds, which is one of the thrust areas in the field of biochemistry and pharmacy and can be used to cure obesity, diabetes, and cancer all at once.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Achari, A.E.; Jain, S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. *Int. J. Molecular. Sci*.**2017**, *18*, https://doi.org/10.3390/ijms18061321.
2. Iwabu, M.; Okada-Iwabu, M.; Yamauchi, T.; Kadowaki, T. Adiponectin/AdipoR research and its implications for lifestyle-related diseases. *Front. Cardiovascular Med.***2019**, *6*, https://doi.org/10.3389/fcvm.2019.00116.
3. Robinson, K.; Prins, J.; Venkatesh, B. Clinical review: adiponectin biology and its role in inflammation and critical illness. *Crit. Care***2011**, *15*, https://doi.org/10.1186/cc10021.
4. Esmaili, S.; Hemmati, M.; Karamian, M. Physiological role of adiponectin in different tissues: a review. *Arch. PhysiolBiochem.***2020**, *126*, 67-73,https://doi.org/10.1080/13813455.2018.1493606.
5. Ryo, M.; Nakamura, T.; Kihara, S.; Kumada, M.; Shibazaki, S.; Takahashi, M.; Nagai, M.; Matsuzawa, Y.; Funahashi, T. Adiponectin as a Biomarker of the Metabolic Syndrome. *Circulation Journal* **2004**, *68*, 975-981,https://doi.org/10.1253/circj.68.975.

6. Schraw, T.; Wang, Z.V.; Halberg, N.; Hawkins, M.; Scherer, P.E. Plasma adiponectin complexes have distinct biochemical characteristics. *Endocrinol*. **2008**, *149*, 2270-2282,https://doi.org/10.1210/en.2007-1561.
7. Waki, H.; Yamauchi, T.; Kamon, J.; Ito, Y.; Uchida, S.; Kita, S.; Hara, K.; Hada, Y.; Vasseur, F.; Froguel, P.; Kimura, S.; Nagai, R.; Kadowaki, T. Impaired Multimerization of Human Adiponectin Mutants Associated with Diabetes: Molecular Structure And Multimer Formation Of Adiponectin.*Journal of Biological Chemistry* **2003**, *278*, 40352-40363, https://doi.org/10.1074/jbc.M300365200.
8. Ronsley, R.; Rassekh, S.R.; Fleming, A.; Empringham, B.; Jennings, W.; Portwine, C.; Burrow, S.; Zelcer, S.; Johnston, D.L.; Thabane, L.; Samaan, M.C. High molecular weight adiponectin levels are inversely associated with adiposity in pediatric brain tumor survivors. *Scientific Reports* **2020**, *10*, 1-8,https://doi.org/10.1038/s41598-020-75638-w.
9. Zhu, N.; Pankow, J.S.; Ballantyne, C.M.; Couper, D.; Hoogeveen, R.C.; Pereira, M.; Duncan, B.B.; Schmidt, M.I.s. High-Molecular-Weight Adiponectin and the Risk of Type 2 Diabetes in the ARIC Study. *The Journal of Clinical Endocrinology & Metabolism* **2010**, *95*, 5097-5104,https://doi.org/10.1210/jc.2010-0716.
10. Ouchi, N.; Walsh, K. Adiponectin as an anti-inflammatory factor. *Clinica Chimica Acta***2010**, *380*, 24-30,https://doi.org/10.1016/j.cca.2007.01.026.
11. Khanal, P.; Chawla, U.; Praveen, S.; Malik, Z.; Malik, S.; Yusuf, M.; Khan, S.A.; Sharma, M. Study of Naturally-derived Biomolecules as Therapeutics against SARS-CoV-2 Viral Spike Protein. *J. Pharmaceut. Res. Int.* **2021**, *33*, 211-220,https://doi.org/10.9734/jpri/2021/v33i28A31524.
12. Gruber, S.; Omann, M.; Zeilinger, S. Comparative analysis of the repertoire of G protein-coupled receptors of three species of the fungal genus *Trichoderma*. *BMC Microbiol*. **2013**, *13*, 1-14,https://doi.org/10.1186/1471-2180-13-108.
13. Bobbert, T.; Rochlitz, H.; Wegewitz, U.; Akpulat, S.; Mai, K.; Weickert, M.O.; Mohlig, M.; Pfeiffer, A.F.H.; Spranger, J. Changes of adiponectin oligomer composition by moderate weight reduction. *Diabetes* **2005**, *54*, 2712-2719,https://doi.org/10.2337/diabetes.54.9.2712.
14. Kyte, J.; Doolittle, R.F. A simple method for displaying the hydropathic character of a protein. *J. Molecular Biology***1982**, *157*, 105-132,https://doi.org/10.1016/0022-2836(82)90515-0.
15. Wang, Y.; Lam, K.S.; Yau, M.H.; Xu, A. Post-translational modifications of adiponectin: mechanisms and functional implications. *Biochem. J.* **2008**, *409*, 623-633,https://doi.org/10.1042/BJ20071492.
16. Briggs, D.B.; Giron, R.M.; Schnittker, K.; Hart, M.V.; Park, C.K.; Hausrath, A.C.; Tsao, T.-S. Zinc enhances adiponectin oligomerization to octadecamers but decreases the rate of disulfide bond formation. *BioMetals* **2012**, *25*, 469-486,https://doi.org/10.1007/s10534-012-9519-9.
17. Briggs, D.B.; Giron, R.M.; Malinowski, P.R.; Nuñez, M.; Tsao, T.S. Role of redox environment on the oligomerization of higher molecular weight adiponectin. *BMC Biochem*. **2011**, *12*, 1-12,https://doi.org/10.1186/1471-2091-12-24.
18. Barbe, A.; Bongrani, A.; Mellouk, N.; Estienne, A.; Kurowska, P.; Grandhaye, J.; Elfassy, Y.; Levy, R.; Rak, A.; Froment, P.; Dupont, J. Mechanisms of Adiponectin Action in Fertility: An Overview from Gametogenesis to Gestation in Humans and Animal Models in Normal and Pathological Conditions. *Int J Mol Sci* **2019**, *20*,https://doi.org/10.3390/ijms20071526.
19. Lappas, M.; Permezel, M.; Rice, G.E. Leptin and adiponectin stimulate the release of proinflammatory cytokines and prostaglandins from human placenta and maternal adipose tissue via nuclear factor-κB, peroxisomal proliferator-activated receptor-γ and extracellularly regulated kinase 1/2. *Endocrinol*. **2005**, *146*, 3334-3342,https://doi.org/10.1210/en.2005-0406.
20. Denzel, M.S.; Scimia, M.C.; Zumstein, P.M.; Walsh, K.; Ruiz-Lozano, P.; Ranscht, B. T-cadherin is critical for adiponectin-mediated cardioprotection in mice. *The J. Clin. Invest*. **2010**, *120*, 4342-4352,https://doi.org/10.1172/JCI43464.
21. Cheng, Z.; White, M.F. Targeting Forkhead box O1 from the concept to metabolic diseases: lessons from mouse models. *Antioxidants Redox Signal.* **2011**, *14*, 649-661,https://doi.org/10.1089/ars.2010.3370.
22. Tanabe, H.; Fujii, Y.; Okada-Iwabu, M.; Iwabu, M.; Kano, K.; Kawana, H.; Hato, M.; Nakamura, Y.; Terada, T.; Kimura-Someya, T.; Shirouzu, M.; Kawano, Y.; Yamamoto, M.; Aoki, J.; Yamauchi, T.; Kadowaki, T.; Yokoyama, S. Human adiponectin receptor AdipoR1 assumes closed and open structures. *Communications Biology* **2020**, *3*,https://doi.org/10.1038/s42003-020-01160-4.
23. Deepa, S.S.; Dong, L.Q. APPL1: role in adiponectin signaling and beyond. *American Journal of Physiology-Endocrinology and Metabolism* **2009**, *296*, E22-E36,https://doi.org/10.1152/ajpendo.90731.2008.
24. Kim, Y.; Park, C.W. Mechanisms of adiponectin action: implication of adiponectin receptor agonism in diabetic kidney disease. *Int. J. Mol. Sci*.**2019**, *20*, https://doi.org/10.3390/ijms20071782.
25. Luo, J.L.; Kamata, H.; Karin, M. IKK/NF-κB signaling: balancing life and death–a new approach to cancer therapy. *The J. Clin. Invest*. **2005**, *115*, 2625-2632,https://doi.org/10.1172/JCI26322.
26. Sugiyama, M.; Takahashi, H.; Hosono, K.; Endo, H.; Kato, S.; Yoneda, K.; Nozaki, Y.; Fujita, K.; Yoneda, M.; Wada, K.; Nakagama, H.; Nakajima, A. Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. *Int J Oncol* **2009**, *34*, 339-344,https://doi.org/10.3892/ijo_00000156.
27. Yan, W.; Zhang, H.; Liu, P.; Wang, H.; Liu, J.; Gao, C.; Liu, Y.; Lian, K.; Yang, L.; Sun, L.; Guo, Y.; Zhang, L.; Dong, L.; Lau, W.B.; Gao, E.; Gao, F.; Xiong, L.; Wang, H.; Qu, Y.; Tao, L. Impaired mitochondrial

biogenesis due to dysfunctional adiponectin-AMPK-PGC-1α signaling contributing to increased vulnerability in diabetic heart. *Basic Research in Cardiology* **2013**, *108*,https://doi.org/10.1007/s00395-013-0329-1.
28. Gan, L.; Yan, J.; Liu, Z.; Feng, M.; Sun, C. Adiponectin prevents reduction of lipid-induced mitochondrial biogenesis via AMPK/ACC2 pathway in chicken adipocyte. *J. Cellular Biochem.***2015**, *116*, 1090-1100,https://doi.org/10.1002/jcb.25064.
29. Tessneer, K.L.; Jackson, R.M.; Griesel, B.A.; Olson, A.L. Rab5 activity regulates GLUT4 sorting into insulin-responsive and non-insulin-responsive endosomal compartments: a potential mechanism for development of insulin resistance. *Endocrinol*.**2014**, *155*, 3315-3328,https://doi.org/10.1210/en.2013-2148.
30. Hug, C.; Wang, J.; Ahmad, N.S.; Bogan, J.S.; Tsao, T.S.; Lodish, H.F. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin.*Proceed. National Acad. Sci.***2004**, *101*, 10308-10313,https://doi.org/10.1073/pnas.0403382101.
31. Fujishima, Y.; Maeda, N.; Matsuda, K.; Masuda, S.; Mori, T.; Fukuda, S.; Sekimoto, R.; Yamaoka, M.; Obata, Y.; Kita, S.; Nishizawa, H.; Funahashi, T.; Ranscht, B.; Shimomura, I. Adiponectin association with T-cadherin protects against neointima proliferation and atherosclerosis. *The FASEB Journal* **2017**, *31*, 1571-1583,https://doi.org/10.1096/fj.201601064R.
32. Frismantiene, A.; Dasen, B.; Pfaff, D.; Erne, P.; Resink, T.J.; Philippova, M. T-cadherin promotes vascular smooth muscle cell dedifferentiation via a GSK3β-inactivation dependent mechanism. *Cellular Signal*. **2016**, *28*, 516-530,https://doi.org/10.1016/j.cellsig.2016.02.014.
33. Shibata, R.; Ouchi, N.; Ohashi, K.; Murohara, T. The role of adipokines in cardiovascular disease. *J. Cardiol*.**2017**, *70*, 329-334,https://doi.org/10.1016/j.jjcc.2017.02.006.
34. Xydakis, A.M.; Case, C.C.; Jones, P.H.; Hoogeveen, R.C.; Liu, M.-Y.; Smith, E.O.B.; Nelson, K.W.; Ballantyne, C.M. Adiponectin, Inflammation, and the Expression of the Metabolic Syndrome in Obese Individuals: The Impact of Rapid Weight Loss through Caloric Restriction. *The Journal of Clinical Endocrinology & Metabolism* **2004**, *89*, 2697-2703,https://doi.org/10.1210/jc.2003-031826.
35. Astapova, O.; Leff, T. Adiponectin and PPARγ: cooperative and interdependent actions of two key regulators of metabolism. *Vitamins Hormones***2012**, *90*, 143-162.https://doi.org/10.1016/B978-0-12-398313-8.00006-3.
36. Bouskila, M.; Pajvani, U.B.; Scherer, P.E. Adiponectin: a relevant player in PPAR γ-agonist-mediated improvements in hepatic insulin sensitivity? *Int. J. Obesity***2005**, *29*, S17-S23,https://doi.org/10.1038/sj.ijo.0802908.
37. Govindarajulu, M.; Pinky, P.D.; Bloemer, J.; Ghanei, N.; Suppiramaniam, V.; Amin, R. Signaling mechanisms of selective PPARγ modulators in Alzheimer's disease. *PPAR Res*. **2018**, *2018*, 1-20,https://doi.org/10.1155/2018/2010675.
38. Ciavarella, C.; Motta, I.; Valente, S.; Pasquinelli, G. Pharmacological (or synthetic) and nutritional agonists of PPAR-γ as candidates for cytokine storm modulation in COVID-19 disease. *Molecules***2020**, *25*,https://doi.org/10.3390/molecules25092076.
39. Tsuchida, A.; Yamauchi, T.; Takekawa, S.; Hada, Y.; Ito, Y.; Maki, T.; Kadowaki, T. Peroxisome proliferator-activated receptor (PPAR)alpha activation increases adiponectin receptors and reduces obesity-related inflammation in adipose tissue: comparison of activation of PPARalpha, PPARgamma, and their combination. *Diabetes* **2005**, *54*, 3358-3370,https://doi.org/10.2337/diabetes.54.12.3358.
40. Chawla, U.; Perera, S.M.D.C.; Fried, S.D.E.; Eitel, A.R.; Mertz, B.; Weerasinghe, N.; Pitman, M.C.; Struts, A.V.; Brown, M.F. Activation of the G-Protein-Coupled Receptor Rhodopsin by Water. *Angewandte Chemie International Edition* **2021**, *60*, 2288-2295,https://doi.org/10.1002/anie.202003342.
41. Hutchinson, D.S.; Summers, R.J.; Bengtsson, T. Regulation of AMP-activated protein kinase activity by G-protein coupled receptors: potential utility in treatment of diabetes and heart disease. *Pharmacol. Therapeut*.**2008**, *119*, 291-310,https://doi.org/10.1016/j.pharmthera.2008.05.008.
42. Jungtrakoon, P.; Plengvidhya, N.; Tangjittipokin, W.; Chimnaronk, S.; Salaemae, W.; Chongjaroen, N.; Chanprasert, K.; Sujjitjoon, J.; Srisawat, C.; Yenchitsomanus, P.-t. Novel Adiponectin Variants Identified in Type 2 Diabetic Patients Reveal Multimerization and Secretion Defects. *PloS one* **2011**, *6*, https://doi.org/10.1371/journal.pone.0026792.
43. Ma, L.; Zhang, Z.; Xue, X.; Wan, Y.; Ye, B.; Lin, K. A potent peptide as adiponectin receptor 1 agonist to against fibrosis. *J. Enzyme Inhibit. Med. Chem.***2017**, *32*, 624-631,https://doi.org/10.1080/14756366.2017.1284067.
44. Muratore, M.; Komai, A.M. Theoretical study of the adiponectin receptors: binding site characterization and molecular dynamics of possible ligands for drug design. *SN Appl. Sci*.**2020**, *2*, 1-14,https://doi.org/10.1007/s42452-020-2333-z.
45. Okada-Iwabu, M.; Yamauchi, T.; Iwabu, M.; Honma, T.; Hamagami, K.-i.; Matsuda, K.; Yamaguchi, M.; Tanabe, H.; Kimura-Someya, T.; Shirouzu, M. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature***2013**, *503*, 493-499,https://doi.org/10.4093/dmj.2015.39.5.363.
46. Kim, S.; Lee, Y.; Kim, J.W.; Son, Y.-J.; Ma, M.J.; Um, J.-H.; Kim, N.D.; Min, S.H.; Kim, D.I.; Kim, B.B. Discovery of a novel potent peptide agonist to adiponectin receptor 1. *PloS one* **2018**, *13*, https://doi.org/10.1371/journal.pone.0199256.
47. Tanabe, H.; Fujii, Y.; Okada-Iwabu, M.; Iwabu, M.; Nakamura, Y.; Hosaka, T.; Motoyama, K.; Ikeda, M.; Wakiyama, M.; Terada, T.; Ohsawa, N.; Hato, M.; Ogasawara, S.; Hino, T.; Murata, T.; Iwata, S.; Hirata, K.;

Kawano, Y.; Yamamoto, M.; Kimura-Someya, T.; Shirouzu, M.; Yamauchi, T.; Kadowaki, T.; Yokoyama, S. Crystal structures of the human adiponectin receptors. *Nature* **2015**, *520*, 312-316,https://doi.org/10.1038/nature14301.
48. Ghaffar, A.; Batool, S.; Mushtaq, G.; Kamal, M. In silico Analysis of AMP-activated Protein Kinase and Ligand-based Virtual Screening for Identification of Novel AMPK Activators.*Cur. Computer-aided Drug Design***2017**, *13*, 222-233,https://doi.org/10.2174/1573409913666170309144722.
49. Li, Y.; Peng, J.; Li, P.; Du, H.; Li, Y.; Liu, X.; Zhang, L.; Wang, L.-L.; Zuo, Z. Identification of potential AMPK activator by pharmacophore modeling, molecular docking and QSAR study. *Computational Biology and Chemistry* **2019**, *79*, 165-176,https://doi.org/10.1016/j.compbiolchem.2019.02.007.
50. Hao, J.; Yang, Z.; Li, J.; Han, L.; Zhang, Y.; Wang, T. Discovery of natural adenosine monophosphate-activated protein kinase activators through virtual screening and activity verification studies. *Mol. Med. Rep*. **2021**, *23*, 1-10,https://doi.org/10.3892/mmr.2021.11842.
51. Kung, J.; Henry, R.R. Thiazolidinedione safety. *Expert Opin. Drug Safety***2012**, *11*, 565-579,https://doi.org/10.1517/14740338.2012.691963.
52. Encinar, J.A.; Fernández-Ballester, G.; Galiano-Ibarra, V.; Micol, V. In silico approach for the discovery of new PPARγ modulators among plant-derived polyphenols. *Drug Design, Develop Therapy***2015**, *9*, 5877-5886,https://doi.org/10.2147/DDDT.S93449.
53. Selvaraj, G.; Kaliamurthi, S.; Thirugnanasambandam, R. Molecular docking studies on potential PPAR-γ agonist from Rhizophora apiculata. *Bangladesh J. Pharmacol.***2014**, *9*, 298-302,https://doi.org/10.3329/bjp.v9i3.18915.
54. Adibian, M.; Hodaei, H.; Nikpayam, O.; Sohrab, G.; Hekmatdoost, A.; Hedayati, M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *Phytother. Res*. **2019**, *33*, 1374-1383, https://doi.org/10.1002/ptr.6328.
55. Ugwu, D.I.; Okoro, U.C.; Mishra, N.K.; Okafor, S.N. Novel Phenoxazinones as potent agonist of PPAR-α: design, synthesis, molecular docking and in vivo studies. *Lipids Health Dis.***2018**, *17*, https://doi.org/10.1186/s12944-018-0764-y.
56. Kim, S.O.; Han, Y.; Ahn, S.; An, S.; Shin, J.C.; Choi, H.; Kim, H.-J.; Park, N.H.; Kim, Y.-J.; Jin, S.H.; Rho, H.S.; Noh, M. Kojyl cinnamate esters are peroxisome proliferator-activated receptor α/γ dual agonists. *Bioorganic & Medicinal Chemistry* **2018**, *26*, 5654-5663,https://doi.org/10.1016/j.bmc.2018.10.010.
57. Lim, S.; Quon, M.J.; Koh, K.K. Modulation of adiponectin as a potential therapeutic strategy. *Atherosclerosis***2014**, *233*, 721-728,https://doi.org/10.1016/j.atherosclerosis.2014.01.051.
58. Abou-Samra, M.; Selvais, C.M.; Dubuisson, N.; Brichard, S.M. Adiponectin and Its Mimics on Skeletal Muscle: Insulin Sensitizers, Fat Burners, Exercise Mimickers, Muscling Pills or Everything Together? *Int. J. Mol. Sci*.**2020**, *21*, 2620-2635,https://doi.org/10.3390/ijms21072620.
59. Weidner, C.; Wowro, S.J.; Freiwald, A.; Kawamoto, K.; Witzke, A.; Kliem, M.; Siems, K.; Müller-Kuhrt, L.; Schroeder, F.C.; Sauer, S. Amorfrutin B is an efficient natural peroxisome proliferator-activated receptor gamma (PPARγ) agonist with potent glucose-lowering properties. *Diabetologia* **2013**, *56*, 1802-1812, https://doi.org/10.1007/s00125-013-2920-2.
60. Xu, A.; Wang, H.; Hoo, R.L.C.; Sweeney, G.; Vanhoutte, P.M.; Wang, Y.; Wu, D.; Chu, W.; Qin, G.; Lam, K.S.L. Selective elevation of adiponectin production by the natural compounds derived from a medicinal herb alleviates insulin resistance and glucose intolerance in obese mice. *Endocrinol*.**2009**, *150*, 625-633,https://doi.org/10.1210/en.2008-0999.
61. Wang, X.; Wang, Y.; Hu, J.-P.; Yu, S.; Li, B.-K.; Cui, Y.; Ren, L.; Zhang, L.-D. Astragaloside IV, a natural PPARγ agonist, reduces Aβ production in alzheimer's disease through inhibition of BACE1.*Mol. Neurobiol*.**2017**, *54*, 2939-2949,https://doi.org/10.1007/s12035-016-9874-6.
62. Wang, L.; Waltenberger, B.; Pferschy-Wenzig, E.-M.; Blunder, M.; Liu, X.; Malainer, C.; Blazevic, T.; Schwaiger, S.; Rollinger, J.M.; Heiss, E.H.; Schuster, D.; Kopp, B.; Bauer, R.; Stuppner, H.; Dirsch, V.M.; Atanasov, A.G. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): a review. *Biochemical Pharmacology* **2014**, *92*, 73-89,https://doi.org/10.1016/j.bcp.2014.07.018.
63. Takeshita, M. Congress: 70th Scientific Sessions. A Catechin-Rich Beverage with No Caffeine Ameliorates Body Fat and Circulating High-Molecular Weight Adiponectin (HMW-Ad) in Overweight/Obese Men. **2010.**Available at https://professional.diabetes.org/abstract/catechin-rich-beverage-no-caffeine-ameliorates-body-fat-and-circulating-high-molecular(Retrieved 23.11.2021).
64. Teixeira, D.; Pestana, D.; Faria, A.; Calhau, C.; Azevedo, I.; Monteiro, R. Modulation of adipocyte biology by Δ9-tetrahydrocannabinol. *Obesity***2010**, *18*, 2077-2085,https://doi.org/10.1038/oby.2010.100.
65. de Groot, J.C.; Weidner, C.; Krausze, J.; Kawamoto, K.; Schroeder, F.C.; Sauer, S.; Büssow, K. Structural Characterization of Amorfrutins Bound to the Peroxisome Proliferator-Activated Receptor γ. *Journal of Medicinal Chemistry* **2013**, *56*, 1535-1543,https://doi.org/10.1021/jm3013272.
66. Li, L.; Gan, H.; Jin, H.; Fang, Y.; Yang, Y.; Zhang, J.; Hu, X.; Chu, L. Astragaloside IV promotes microglia/macrophages M2 polarization and enhances neurogenesis and angiogenesis through PPARγ pathway after cerebral ischemia/reperfusion injury in rats. *Int. Immunopharmacol*. **2021**, *92*, https://doi.org/10.1016/j.intimp.2020.107335.

67. Cao, Y.; Lv, Q. and Li, Y. Astragaloside IV Improves Tibial Defect in Rats and Promotes Proliferation and Osteogenic Differentiation of hBMSCs through MiR-124-3p. 1/STAT3 Axis. *J. Nat. Prod.***2021**, *84*, 287-297,https://doi.org/10.1021/acs.jnatprod.0c00975.
68. Yarmohammadi, F.; Hayes, A.W.; Karimi, G. Natural and chemical compounds as protective agents against cardiac lipotoxicity. *Biomed. Pharmacother*. **2022**, *145*, https://doi.org/10.1016/j.biopha.2021.112413.
69. Zhang, Y.; Wang, Y.; Ding, J. and Liu, P. Efferocytosis in multisystem diseases. *Mol. Med. Rep*. **2022**, *25*, 1-15,https://doi.org/10.3892/mmr.2021.12529.
70. Zheng, S.; Huang, H.; Li, Y.; Wang, Y.; Zheng, Y.; Liang, J.; Zhang, S.; Liu, M.; Fang, Z. Yin-xing-tong-mai decoction attenuates atherosclerosis via activating PPARγ-LXRα-ABCA1/ABCG1 pathway. *Pharmacolog. Res.***2021**, *169*,https://doi.org/10.1016/j.phrs.2021.105639.
71. Tanaka, E.; Mitani, T.; Nakashima, M.; Yonemoto, E.; Fujii, H.; Ashida, H. Theobromine enhances the conversion of white adipocytes into beige adipocytes in a PPARγ activation-dependent manner. *The J. Nutr. Biochem*. **2022**, *100*, https://doi.org/10.1016/j.jnutbio.2021.108898.
72. Swamy, G.M.; Ramesh, G.; Prasad, R.D.; Meriga, B. Astragalin(3-O-glucoside of kaempferol), isolated from Moringa oleifera leaves modulates leptin, adiponectin secretion and inhibits adipogenesis in 3T3-L1 adipocytes.*Arch. Physiol. Biochem: The J. Metabolic Dis.***2020**,https://doi.org/10.1080/13813455.2020.1740742.
73. Knezevic, S.; Ghafoor, A.; Mehri, S.; Barazi, A.; Dziura, M.; Trant, J.F.; Dieni C.A. Catechin and other catechol-containing secondary metabolites: Bacterial biotransformation and regulation of carbohydrate metabolism. *PharmaNutr.***2021**, *11*, https://doi.org/10.1016/j.phanu.2021.100273.
74. Ko, H.; Jang, H.; An, S.; Park, I.G.; Ahn, S.; Gong, J.; Hwang, S.Y.; Oh, S.; Kwak, S.Y.; Choi, W.J.; Kim, H.; Noh, M. Galangin 3-benzyl-5-methylether derivatives function as an adiponectin synthesis-promoting peroxisome proliferator-activated receptor γ partial agonist. *Bioorganic & Medicinal Chemistry* **2022**, *54*,https://doi.org/10.1016/j.bmc.2021.116564.
75. Gravandi, M.M.; Fakhri, S.; Zarneshan, S.N.; Yarmohammadi, A.; Khan, H. Flavonoids modulate AMPK/PGC-1α and interconnected pathways toward potential neuroprotective activities. *Metabolic Brain Dis.***2021**, *36*, 1501–1521,https://doi.org/10.1007/s11011-021-00750-3.
76. Rezvan, N.; Moini, A.; Janani, L.; Mohammad, K.; Saedisomeolia, A.; Nourbakhsh, M.; Gorgani-Firuzjaee, S.; Mazaherioun, M.; Hosseinzadeh-Attar, M.J. Effects of Quercetin on Adiponectin-Mediated Insulin Sensitivity in Polycystic Ovary Syndrome: A Randomized Placebo-Controlled Double-Blind Clinical Trial. *Horm Metab Res* **2017**, *49*, 115-121,https://doi.org/10.1055/s-0042-118705.
77. Jiang, Z.; Yang, Z.; Zhang, H.; Yao, Y.; Ma, H. Genistein activated adenosine 5′-monophosphate-activated protein kinase–sirtuin1/peroxisome proliferator-activated receptor γ coactivator-1α pathway potentially through adiponectin and estrogen receptor β signaling to suppress fat deposition in broiler chickens. *Poultry Sci.***2021**, *100*, 246-255,https://doi.org/10.1016/j.psj.2020.10.013.
78. Goto, T.; Takahashi, N.; Kato, S.; Kim, Y.-I.; Kusudo, T.; Taimatsu, A.; Egawa, K.; Kang, M.-S.; Hiramatsu, T.; Sakamoto, T.; Uemura, T.; Hirai, S.; Kobayashi, M.; Horio, F.; Kawada, T. Bixin Activates PPARα and Improves Obesity-Induced Abnormalities of Carbohydrate and Lipid Metabolism in Mice. *Journal of Agricultural and Food Chemistry* **2012**, *60*, 11952-11958,https://doi.org/10.1021/jf303639f.
79. Suzuki, K.; Inoue, T.; Hashimoto, S.; Ochiai, J.; Kusuhara, Y.; Ito, Y.; Hamajima, N. Association of serum carotenoids with high molecular weight adiponectin and inflammation markers among Japanese subjects. *Clinica Chimica Acta* **2010**, *411*, 1330-1334,https://doi.org/10.1016/j.cca.2010.05.029.
80. Rigano, D.; Sirignano, C.; Taglialatela-Scafati, O. The potential of natural products for targeting PPARα. *Acta Pharmaceutica Sinica B***2017**, *7*, 427-438,https://doi.org/10.1016/j.apsb.2017.05.005.
81. Xiong, H.; Wang, J.; Ran, Q.; Lou, G.; Peng, C.; Gan, Q.; Hu, J.; Sun, J.; Yao, R.; Juang, Q. Hesperidin: a therapeutic agent for obesity. *Drug design, Develop Therapy***2019**, *13*, 3855-3867,https://doi.org/10.2147/DDDT.S227499.
82. Tiss, M.; Souiy, Z.; Achour, L. and Hamden, K. Ephedra alata extracts exerts anti-obesity, anti-hyperglycemia, anti-antipyretic and analgesic effects. *Nutr. Food Sci*. **2021**, *52*,https://doi.org/10.1108/NFS-03-2021-0086.
83. Choudhary, S.; Kaurav, H.; Chaudhary, G. Medicinal importance of in ayurveda and modern sciences: A *Ephedra gerardiana*. *Asian J. Pharmacy Pharmacol*. **2021**, *7*, 110-117,https://doi.org/10.31024/ajpp.2021.7.3.1.
84. Sargin, S.A. Plants used against obesity in Turkish folk medicine: A review. *J. Ethnopharmacol*. **2021**,*270*,https://doi.org/10.1016/j.jep.2021.113841.
85. Horiba, T.; Nishimura, I.; Nakai, Y.; Abe, K.; Sato, R. Naringenin chalcone improves adipocyte functions by enhancing adiponectin production. *Mol. Cellular Endocrinol.***2010**, *323*, 208-214,https://doi.org/10.1016/j.mce.2010.03.020.
86. Yusuf, M.; Shabbir, M.; Mohammad, F. Natural colorants: Historical, processing and sustainable prospects. *Nat. Prod. Bioprospect*. **2017**, *7*, 123-145,https://doi.org/10.1007/s13659-017-0119-9.
87. Akter, R.; Rahman, H.; Behl, T.; Chowdhury, M.; Rahman, A.; Manirujjaman, M.; Bulbul, J.I.; Elshenaw, S.E.; Tit, D.M.; Bunganu, S. Prospective role of polyphenolic compounds in the treatment of

neurodegenerative diseases. *CNS & Neurolog. Disorders-Drug Targets***2021**, *20*, 430-450,https://doi.org/10.2174/1871527320666210218084444.
88. Yusuf, M.; Mohammad, F.; Shabbir, M. Eco-friendly and effective dyeing of wool with anthraquinone colorants extracted from Rubia cordifolia roots: Optimization, colorimetric and fastness assay. *J. King Saud Univ-Sci.***2017**, *29*, 137-144,https://doi.org/10.1016/j.jksus.2016.06.005.
89. Yusuf, M.; Khan, M.A.; Mohammad, F. Investigations of the colourimetric and fastness properties of wool dyed with colorants extracted from Indian madder using reflectance spectroscopy. *Optik: Int. J. Light Electron Optics***2016**, *127*, 6087-6093,https://doi.org/10.1016/j.ijleo.2016.04.084.
90. Liu, Y.; Sun, M.; Yao, H.; Liu, Y.; Gao, R. Herbal medicine for the treatment of obesity: an overview of scientific evidence from 2007 to 2017. *Evidence-Based Complem. Alternat. Med.***2017**, *2017*, 1-17,https://doi.org/10.1155/2017/8943059.
91. Salahshooh, M.M.; Parizadeh, S.M.R.; Pasdar, A.; Saberi Karimian, M.; Safarian, H.; Javandoost, A.; Ferns, G.A.; Ghayour-Mobarhan, M.; Sahebkar, A. The effect of curcumin (Curcuma longa L.) on circulating levels of adiponectin in patients with metabolic syndrome. *Comparative Clinical Pathology* **2017**, *26*, 17-23,https://doi.org/10.1007/s00580-016-2339-5.
92. Nigro, E.; Scudiero, O.; Monaco, M.L.; Palmieri, A.; Mazzarella, G.; Costagliola, C.; Bianco, A.; Daniele, A. New Insight into Adiponectin Role in Obesity and Obesity-Related Diseases. *BioMed research international* **2014**, *2014*, 1-14,https://doi.org/10.1155/2014/658913.
93. Unuofin, J.O.; Masuku, N.P.; Paimo, O.K.; Lebelo, S.L. Ginger from Farmyard to Town: Nutritional and Pharmacological Applications. *Frontiers in Pharmacology* **2021**, *12*,https://doi.org/10.3389/fphar.2021.779352.
94. Adegbola, P.I.; Fadahunsi, O.S.; Ajilore, B.S.; Akintola, A.O. and Olorunnisola, O.S. Combined ginger and garlic extract improves serum lipid profile, oxidative stress markers and reduced IL-6 in diet induced obese rats. *Obesity Med*. **2021**, *23*, https://doi.org/10.1016/j.obmed.2021.100336.
95. Sharma, P.; Singh, S.; Thakur, V.; Sharma, N.; Grewal, A.S. Novel and emerging therapeutic drug targets for management of type 2 Diabetes Mellitus. *Obesity Medicine* **2021**, *23*,https://doi.org/10.1016/j.obmed.2021.100329.
96. Zurbau, A.; Smircic Duvnjak, L.; Magas, S.; Jovanovski, E.; Miocic, J.; Jenkins, A.L.; Jenkins, D.J.A.; Josse, R.G.; Leiter, L.A.; Sievenpiper, J.L.; Vuksan, V. Co-administration of viscous fiber, Salba-chia and ginseng on glycemic management in type 2 diabetes: a double-blind randomized controlled trial. *European Journal of Nutrition* **2021**, *60*, 3071-3083,https://doi.org/10.1007/s00394-020-02434-7.
97. Wang, Q.; Li, C.; Cao, Z.; Yang, X. Network-based analysis of Jinfukang in the treatment of lung cancer. *European Journal of Integrative Medicine* **2021**, *41*,https://doi.org/10.1016/j.eujim.2020.101232.
98. Aghaei, F.; Moradi, M.T.; Karimi, A. Punicalagin inhibits pro-inflammatory cytokines induced by influenza A virus. *European Journal of Integrative Medicine* **2021**, *43*,https://doi.org/10.1016/j.eujim.2021.101324.
99. Basist, P.; Parveen, B.; Zahiruddin, S.; Gautam, G.; Parveen, R.; Khan, M.A.; Krishnan, A.; Shahid, M.; Ahmad, S. Potential nephroprotective phytochemicals: Mechanism and future prospects. *Journal of Ethnopharmacology* **2022**, *283*,https://doi.org/10.1016/j.jep.2021.114743.
100. Chawla, U.; Kashyap, M.K.; Husain, A.. Aging and diabetes drive the COVID-19 forwards; unveiling nature and existing therapies for the treatment. *Molecular and Cellular Biochemistry*, **2021,** *476*(11), 3911-3922. https://doi.org/10.1007/s11010-021-04200-7